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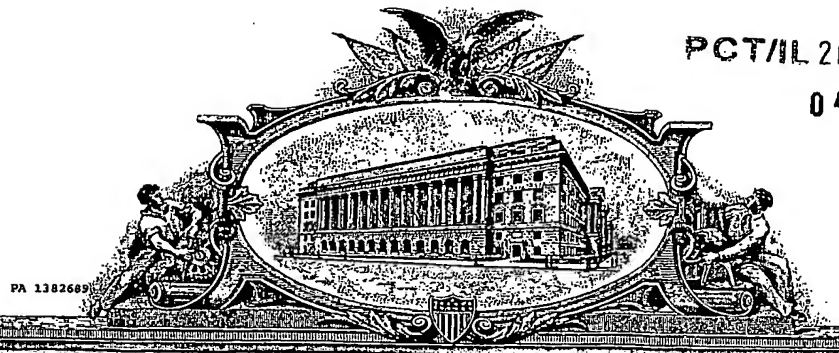

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APPLICATION NUMBER: *60/641,081*
FILING DATE: *January 04, 2005*

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS *US60/641,081*

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a **PROVISIONAL APPLICATION FOR PATENT** under 37 CFR 1.53 (b)(2).

Docket Number	28959	Type a plus sign (+) inside this box ->	+

INVENTOR(s) / APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
HASHIMSHONY	Dan		Givat Ada, Israel

TITLE OF THE INVENTION (280 characters max)

DEVICE AND METHOD FOR TISSUE CHARACTERIZATION IN A BODY LUMEN, BY AN ENDOSCOPIC ELECTROMAGNETIC PROBE

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ 13 pages of specification (including Abstract page)	☐ Assignment to:
☐ ___ pages of sequence listing	☒ 21 Claims
☒ 5 sheets of drawings	☒ Applicant is entitled to Small Entity Status under 37 CFR 1.9 and 37 CFR 1.27
☒ 18 total pages	

THE FILING FEE HAS BEEN CALCULATED AS SHOWN BELOW:

FOR:	SMALL ENTITY RATE	SMALL ENTITY FEE	OTHER THAN A SMALL ENTITY RATE	OTHER THAN A SMALL ENTITY FEE
Provisional Application Filing Fee	1	$ 100		$ 200
Provisional Application Size Fee (Per 50 Pages Over 100)	0 x $ 125	$	x $250	$
	TOTAL	$ 100	TOTAL	$

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☑ Authorization to charge the above filing fee of $100 to the Credit Card number listed on the attached Credit Card Payment Form PTO-2038 is attached herewith. In the event additional fees are required, please charge these additional fees to Deposit Account 50-1407. In the unlikely event payment by the Credit Card issuer is refused, please charge the filing fee of $100 to Deposit Account 50-1407.

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No ☐ Yes, the name of the US Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE Martin J. Moynihan Date 4 January 2005

TYPED or PRINTED NAME Martin Moynihan REGISTRATION NO. 40,338 *(if appropriate)*

☐ Additional inventors are being named on separately numbered sheets attached hereto

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

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APPLICATION FOR PATENT

Inventor: Dan HASHIMSHONY

Title: Device and Method for Tissue Characterization in a Body Lumen, by an Endoscopic Electromagnetic Probe

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to a device and method for tissue characterization in a body lumen, for the detection of abnormalities, using an electromagnetic probe, mounted on an endoscope.

The impact of cancer of the gastrointestinal tract is grave. In spite of enormous expenditures of financial and human resources, early detection of malignant tumors remains an unfulfilled medical goal. While it is known that a number of cancers are treatable if detected at an early stage, lack of reliable screening procedures results in their being undetected and untreated.

Various forms of endoscopes are currently in use. For example, diagnosis of different conditions of the colon generally involves using a colonoscope. A typical colonoscope includes, at its distal end, with respect to an operator, a light source, a video chip, and a suction channel. These elements are all in communication with a proximal end of the colonoscope via wires and channels housed within a flexible tube. The distal end is inserted into a patient's rectum and can be maneuvered along the length of the colon. A colonoscope can be inserted far enough into a patient's colon for the distal end to enter the patient's cecum. The tip of the colonoscope can also be maneuvered through the ileo-cecal valve into the terminal ileum.

A colonoscope provides a visual image only of the region of the colon that is immediately near the light source and video chip, yielding visual information for only a small region of the colon at any given time. Lesions in a patient's colon typically are identified by progressive and painstaking visual examination of the entire colon. However, a single colonoscopy is often not sufficient to identify the source of

colorectal bleeding which is typically sporadic and in many cases would be best located by observing the entire colon over a period of time.

Various attachments to a colonoscope allow small surgical procedures, such as tissue biopsies, to be carried out during a colonoscopic examination.

Endoscopy of the small intestine is also known. For example, U.S. Patent 5,984, 860, to Shan, entitled, "Pass-through duodenal enteroscopic device," whose disclosure is incorporated herein by reference, describes a tethered ingestible, enteroscopic video camera, which utilizes the natural contraction wave of the small intestine to propel it through the small intestine at about the same speed as any other object therein. The video camera includes an illumination source at its forward end. Covering the camera lens and illumination source is a transparent inflatable balloon, adapted to gently expand the small intestine immediately forward the camera for better viewing. A small diameter communication and power cable unwinds through an aperture in the rear of the camera as it moves through the small intestine. Upon completion of movement through the small intestine the cable is automatically separated, permitting the cable to be withdrawn through the stomach and intestine. The camera continues through the large intestine and passes from the patient through the rectum.

The aforementioned endoscopes, while providing means to access and visualize portions of the gastrointestinal track, do not provide means of detecting gastrointestinal pathologies, which are not clearly visible. In particular, they do not provide means for localization and differentiation of occult tumors. Typically, a large tumor is readily located by visualization. Yet, for subsequent operative success, as well as for the success of other forms of treatment, it is necessary to somehow locate tumors in their occult stage, when they cannot be found by sight and feel.

Similarly, lung cancer is the leading cause of cancer death in both men and women in Western society. When detected and treated at an early stage, before it has spread to lymph nodes or other organs, the five-year survival rate is about 42%. However, detection at an early stage is rare. The five-year survival rate for all stages of lung cancer combined is about 14% - a factor of three lower.

Most patients are diagnosed when exhibiting symptoms, for example by bronchoscopy, using an endoscope specifically designed for the lungs. The walls of the bronchial tubes are examined, for example, visually, and small pieces of tissue

may be removed for biopsy. Alternatively, needle aspiration biopsy may be performed, by inserting a needle between the ribs to draw cells from the lung. Alternatively, surgery is performed to remove tissue for biopsy. Diagnosis for malignancy is generally made in a laboratory, on the removed biopsy sample, by examination of the characteristics of the cells under a microscope.

However, biopsy of a sample, with diagnosis performed in a laboratory, suffers from inherent disadvantages, as follows:

i. it is generally performed when symptoms are observed, and the cancer is at an advanced stage;

ii. it may happen that the biopsy is taken from a region near the tumor, and not the tumor itself, leading to erroneous false negative results;

iii. the exact location from which the biopsy was taken, may be difficult to reproduce; and

iv. The results of the biopsy examination are not immediate

Thus, devices and methods for the early detection of cancerous and pre-cancerous tissue, in vivo, are highly desirable.

SUMMARY OF THE INVENTION

The present invention successfully addresses the shortcomings of the presently known configurations by providing a device and method for the detection of abnormalities, using an electromagnetic probe, mounted on an endoscope. The endoscope may be designed for insertion in a body lumen, for example, an oral cavity, a gastrointestinal tract, a rectum, a colon, bronchi, a vagina, a cervix, a urinary tract, blood vessels, or another body lumen. Additionally or alternatively, it may be designed for insertion in a trucar valve.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of the preferred embodiments of the present invention only, and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for a fundamental understanding of the invention, the description taken with the drawings making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

In the drawings:

FIGs. 1A and 1B schematically illustrate an overall endoscopic system, in accordance with the present invention;

FIG. 2 schematically illustrates the intracorporeal portion of the endoscopic system, in accordance with the present invention;

FIGs. 3A – 3C schematically illustrate further the intracorporeal distal tip of the endoscopic system, in accordance with the present invention; and

FIGs. 4A – 4D further illustrate the endoscopic system, in accordance with the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is of a device and method for the detection of abnormalities, using an electromagnetic probe, mounted on an endoscope. The endoscope may be designed for insertion in a body lumen, for example, an oral cavity, a gastrointestinal tract, a rectum, a colon, bronchi, a vagina, a cervix, a urinary tract, blood vessels, or another body lumen. Additionally or alternatively, it may be designed for insertion in a trucar valve.

The principles and operation of the device and method according to the present invention may be better understood with reference to the drawings and accompanying descriptions.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details of

construction and the arrangement of the components set forth in the following description or illustrated in the drawings. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

Referring now to the drawings, Figures 1A and 1B illustrate an overall endoscopic system 10, in accordance with the present invention.

The endoscopic system 10 preferably includes an extracorporeal control station 20, having a control unit 22, a display screen 24, and possibly also, a keyboard 26. The control station 20 may be placed on a rack 28. Alternatively, a hand-held device, or a laptop system, as known, may be used.

Additionally, the endoscopic system 10 includes an endoscope 30, having an extracorporeal portion 34, which preferably includes a manipulator 36, for manipulating the endoscope 30, and a connector 38, for connecting to the extracorporeal control station 20.

Furthermore, the endoscope 30 includes an intracorporeal portion 32, designed for insertion into a body lumen or a trucar valve, and formed as a flexible tubing 40, having a distal tip 42, with respect to an operator (not shown).

The manipulator 36 is preferably, handheld. It may include both mechanical and electrical control features, for controlling the position of the tubing 40 and its tip 42. Preferably, the manipulator 36 may apply to the flexible tubing 40 both lateral motion, as seen by the arrow 31, and rotational motion, as seen by the arrow 33.

Referring further to the drawings, Figure 2 schematically illustrates the intracorporeal portion 32 of the endoscopic system 10, in accordance with the present invention.

Preferably, the flexible tubing 40 of the intracorporeal portion 32 includes an instrument channel 44. Additionally, a sensor 52, mounted on a connection bundle 50, is inserted in the instrument channel 44, preferably, within a catheter 48.

The sensor 52 is an electromagnetic sensor for tissue characterization, for example, as taught in commonly owned US Patent 6,813,515, to Hashimshony, entitled, "Method and system for examining tissue according to the dielectric properties thereof," whose disclosure is incorporated herein by reference. It will be

appreciated that in accordance with the present invention, other electromagnetic sensors may be used.

It will be appreciated that generally, the flexible tubing also includes an optical channel 46, for the optical instrument 43, having an optical connection bundle 45. Preferably, tissue characterization is performed both visually, by the optical instrument 43, and via the sensor 52. However, the present invention may be operable also without the optical channel 46 and without the optical instrument 43.

Referring further to the drawings, Figures 3A – 3C schematically illustrate the intracorporeal distal tip 42 of the endoscopic system 10, in accordance with the present invention.

Preferably, the catheter 48 has a distal tip 47, which may extend beyond the distal tip 42 of the flexible tubing 40. Additionally, the catheter 48 may be manipulated, independent of the tubing 40, via the connection bundle 50, as seen in Figures 3A – 3C, so that the sensor 52 may be brought in contact with a specific location of a tissue 60, such as the inner wall of a body lumen, for example, for characterizing a suspected anomaly 62, as seen in Figures 3A and 3B. The manipulation of the catheter 48 may be mechanical, for example, via wires, or electronic, as known.

Additionally, the sensor 52 may be brought in contact with a healthy portion of the tissue 60, as seen in Figure 3C, for characterization of a reference tissue.

Referring further to the drawings, Figures 4A – 4D further illustrate the endoscope 30, of the endoscopic system 10, in accordance with the present invention.

As seen in Figure 4A, the endoscope 30 may be inserted in a body lumen 64, for characterizing the tissue 60 formed as the walls of the body lumen 64. The insertion may be via a body opening 66, such as a mouth, a nose, or another body opening or orifice.

As seen in Figure 4B, the endoscope 30 may be inserted percutaneously, through a skin 68, and then into the body lumen 64, for characterizing the tissue 60 formed as the walls of the body lumen 64. For example, when the body lumen 64 is a blood vessel.

Additionally, as seen in Figure 4B, the tissue which is characterized may be at a lumen junction 65.

As seen in Figures 4C and 4D, the endoscope 30 may be inserted via a trucar valve 35, through the skin 68, for characterizing the tissue 60, for example, during a minimally invasive surgery.

In accordance with the present invention, the tissue 60, which is characterized by the sensor 52 may be the walls and (or) junctions of the body lumen 64, the walls of other body cavities which may be reached by body lumens, for example, the stomach or the uterus, or open flesh, during a minimally invasive surgery.

In accordance with a first embodiment, the sensor 52 may be guided along the body lumen 64, characterizing the tissue 60, substantially along the full length of it.

Alternatively, the sensor 52 may be guided along the body lumen 64, characterizing the tissue 60, along predetermined portions of it.

Additionally or alternatively, it may happen that the optical instrument 43 detects the suspected anomaly 62, visually, and the sensor 52 is manipulated so as to be brought in contact with the suspected anomaly 62 and characterize it.

Additionally or alternatively, other imaging modalities, such as x-ray, MRI, ultrasound, or another non-invasive modality, detects the suspected anomaly 62, and the sensor 52 is manipulated so as to be brought in contact with it and characterize it.

Alternatively, as seen in Figures 4C and 4D, during a minimally invasive surgery, the sensor 52 may be used in two manners, as follows:

i. for characterizing the tissue 60 and identifying the anomaly 62; and

ii. during the removal of the anomaly 62, by a surgical instrument 70, characterizing a wall of a cut 72, to ensure that it is formed of a healthy tissue, and that the anomaly 62 is contained within.

It will be appreciated that the endoscope 30 may be a multi-channel endoscope, so that several instruments, for example, the optical instrument 43, the sensor 52, and another instrument, for example, the surgical instrument 70 may operate together. Alternatively, only one or two channels may be available, and instruments are pulled out and replaced with other instruments, as needed.

Preferably, the sensor 52 is visible on other imaging modalities such as x-rays, ultrasound and MRI, and may be guided using another imaging modality, so that it can be guided to zones which are not accessible to the optical instrument 43, or in cases where the optical instrument 43 is not used.

Preferably, the catheter 48 is between about 0.5 and about 4 mm in diameter. It will be appreciated that other dimensions, which may be larger or smaller, may similarly be used. Preferably, the sensor 52 is between about 0.4 and about 3 mm in diameter. Again, it will be appreciated that other dimensions, which may be larger or smaller, may similarly be used.

Preferably, the connection bundle is about 2 mm in diameter. Yet other dimensions which may be larger or smaller, may also be used. Preferably the connection bundle includes a power cable, data cables, and mechanical control cable.

The measurement is preferably performed by reflection of electromagnetic fields from the near vicinity of the sensor 52, for example, as taught in commonly owned US Patent 6,813,515, to Hashimshony, entitled, "Method and system for examining tissue according to the dielectric properties thereof," whose disclosure is incorporated herein by reference. It will be appreciated that in accordance with the present invention, other electromagnetic sensors may also be used.

Preferably, the control unit 22 of the extracorporeal control station 20, analyzes the reflection and displays results. It will be appreciated that another computer may be used, as known. The results may be used for characterization of the tissue 60, such as the lumen wall 60, for example, the broncos wall 60, and the anomaly 62. The results may be produced graphically, numerically, or as positive or negative answers. The results may also be presented textually.

The results may be relative, that is a comparison between the anomaly 62 of different types and the reference tissue 60, or several references of the tissue 60 taken from different locations. Alternatively, the results may be based on literary data, in which the tissue is characterized based on previous tests and (or) data found in the literature.

The tissue characterization relating to the anomaly 62 may relate to the detection of a malignancy, or a pre-cancerous state. Additionally or alternatively it may relate to the detection of another pathology, for example, internal bleeding.

In accordance with the present invention, the endoscope 30 may be designed for insertion in a body lumen, for example, an oral cavity, a gastrointestinal tract, a rectum, a colon, bronchi, a vagina, a cervix, a urinary tract, blood vessels, or another body lumen. Additionally or alternatively, it may be designed for insertion in a trucar valve.

It is expected that during the life of this patent many relevant devices and methods for tissue characterization in a body lumen, using an electromagnetic probe, mounted on an endoscopic device, may be developed and the scope of the present invention is intended to include all such new technologies a priori.

As used herein the term "about" refers to ± 20 %.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims.

All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, any citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention.

WHAT IS CLAIMED IS:

1. A device for tissue characterization, comprising:

an endoscope, having a lumen, operative as an instrument channel; and

an electromagnetic sensor for tissue characterization, said sensor having a connection bundle, and said sensor being inserted in said instrument channel.

2. The device of claim 1, wherein said endoscope further includes an optical channel for visual tissue characterization.

3. The device of claim 1, wherein said endoscope is designed for insertion in a body lumen.

4. The device of claim 3, wherein the body lumen is selected from the group consisting of an oral cavity, a gastrointestinal tract, a rectum, a colon, bronchi, a vagina, a cervix, a urinary tract, and blood vessels.

5. The device of claim 1, wherein said endoscope is designed for insertion in a trucar valve.

6. The device of claim 1, wherein tissue characterization relates to the detection of a malignancy.

7. The device of claim 1, wherein tissue characterization relates to the detection of a pre-cancerous state.

8. The device of claim 1, and further including a catheter, wherein said sensor is inserted into said catheter, and said catheter is inserted into said instrument channel.

9. The device of claim 1, wherein said catheter extends beyond a distal-most end of said endoscope, with respect to an operator, and a distal-most end of said catheter may be manipulated independently of said distal-most end of said endoscope.

10. A method for tissue characterization, comprising:

providing an endoscope, having a lumen, operative as an instrument channel; and

inserting an electromagnetic sensor for tissue characterization, having a connection bundle, in said instrument channel.

11. The method of claim 10, wherein said endoscope further includes an optical channel for visual tissue characterization.

12. The method of claim 10, wherein said endoscope is designed for insertion in a body lumen.

13. The method of claim 12, wherein said endoscope is designed for insertion in a body lumen, selected from the group consisting of an oral cavity, a gastrointestinal tract, a rectum, a colon, bronchi, a vagina, a cervix, a urinary tract, and blood vessels.

14. The method of claim 10, wherein said endoscope is designed for insertion in a trucar valve.

15. The method of claim 10, wherein tissue characterization relates to the detection of a malignancy.

16. The method of claim 10, wherein tissue characterization relates to the detection of a pre-cancerous state.

17. The method of claim 10, and further including a catheter, wherein said sensor is inserted into said catheter, and said catheter is inserted into said instrument channel.

18. The method of claim 10, wherein said catheter extends beyond a distal-most end of said endoscope, with respect to an operator, and a distal-most end of said catheter may be manipulated independently of said distal-most end of said endoscope.

19. The method of claim 10, wherein the tissue characterization is performed together with visual observation.

20. The method of claim 10, wherein the tissue characterization is performed together with another modality, selected from the group consisting of x-ray imaging, MRI, and ultrasound.

21. The method of claim 20, wherein said sensor is visible on said another modality.

ABSTRACT OF THE DISCLOSURE

A device and method for tissue characterization in a body lumen, are provided, for the detection of abnormalities, using an electromagnetic probe, mounted on an endoscope. The endoscope may be designed for insertion in a body lumen, for example, an oral cavity, a gastrointestinal tract, a rectum, a colon, bronchi, a vagina, a cervix, a urinary tract, blood vessels, or another body lumen. Additionally or alternatively, it may be designed for insertion in a trucar valve.

Express Mail Label No.

Docket No.
28984

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

METHODS COMPOSITIONS AND ARTICLES OF MANUFACTURE FOR MODULATING BONE GROWTH

the specification of which

☑ is attached hereto.

☐ was filed on _____ as United States Application No. or PCT International Application Number _____

and was amended on _____

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of federal Regulations, Section 1.56. Including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	☐
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	☐

28984

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

60/410,276 (Application Serial No.)	13 September 2002 (Filing Date)
60/385,881 (Application Serial No.)	6 June 2002 (Filing Date)
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U.S.C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112. I acknowledge the duty to disclose to the United States Patent and Trademark Office all the information known to me to be material to patentability as defined in Title 37, C.F.R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

PCT/IL03/00480 (Application Serial No.)	8 June 2003 (Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

28984

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

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Citizenship	:	German
Post Office Address	:	Von-Halberg-Strasse 2, Bonn 53125, Germany

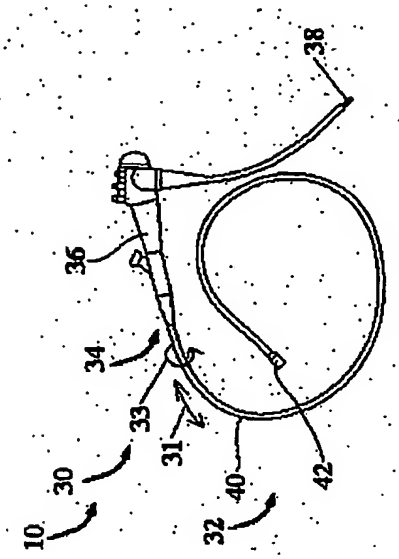

Figure 1B

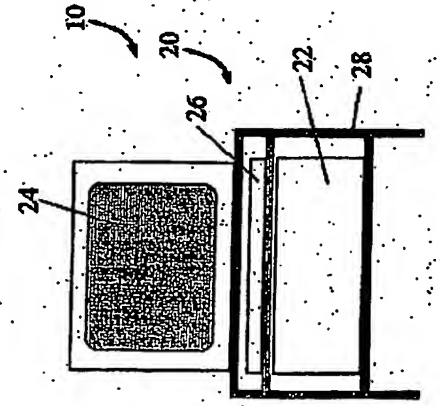

Figure 1A

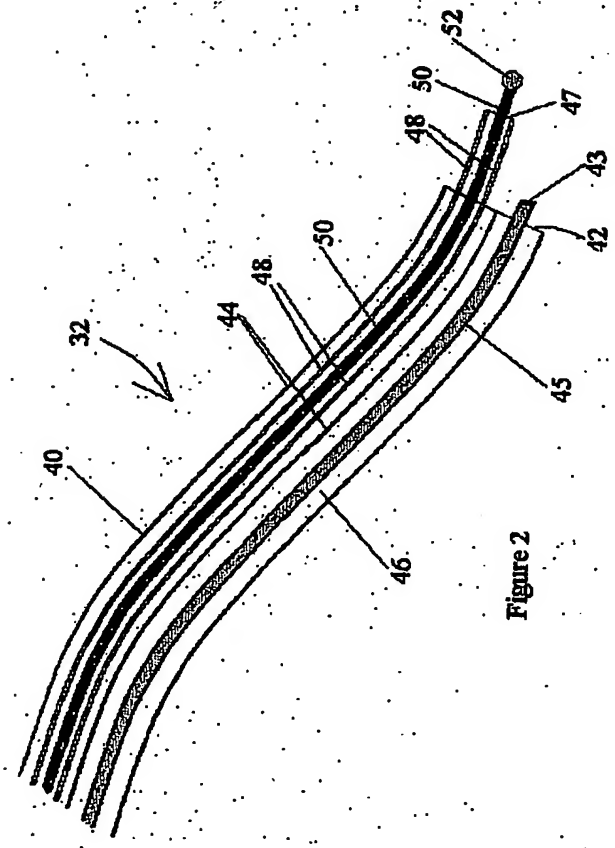

Figure 2

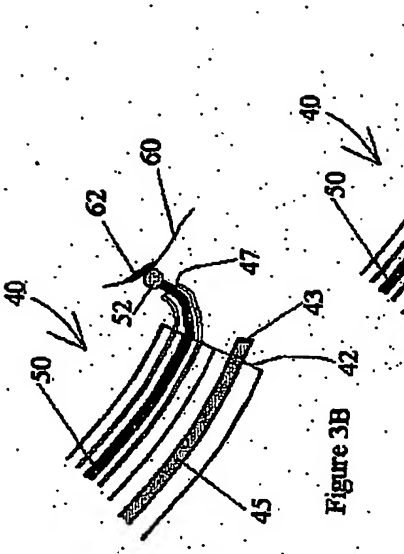

Figure 3B

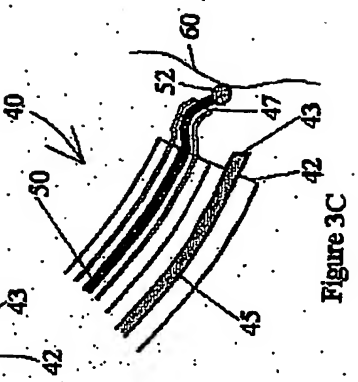

Figure 3C

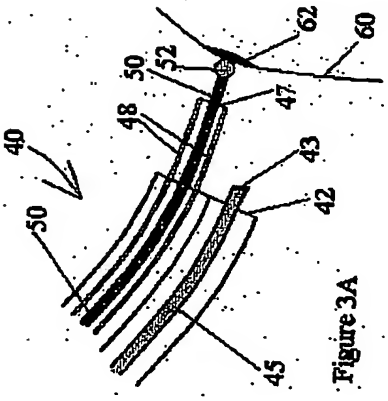

Figure 3A

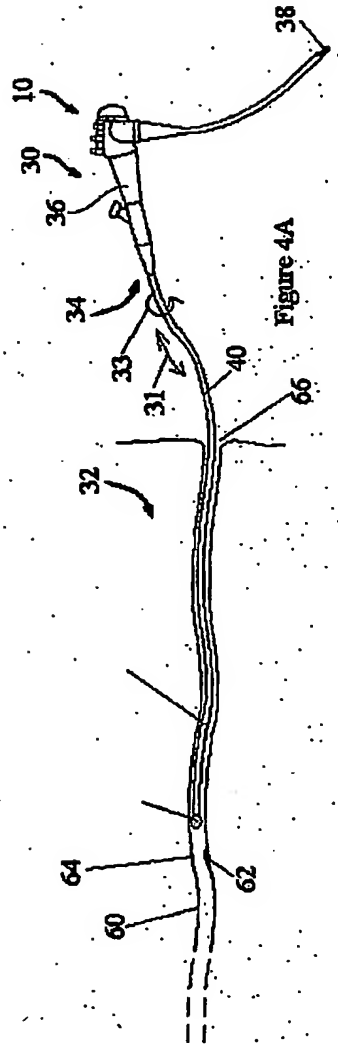

Figure 4A

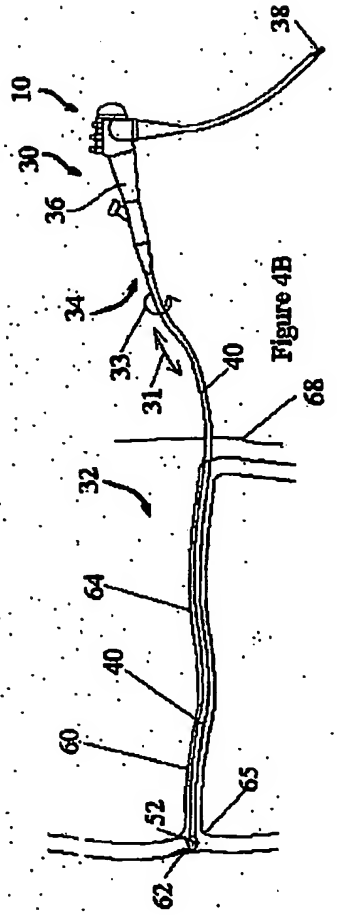

Figure 4B

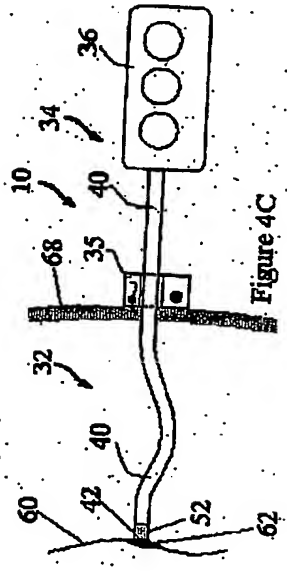

Figure 4C

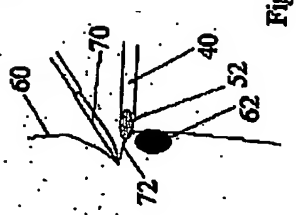

Figure 4D